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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,134	12/18/2006	Pablo Steinberg	101215-219	4520
27387	7590	05/26/2009	EXAMINER	
NORRIS, MC LAUGHLIN & MARCUS, P.A.			STAPLES, MARK	
875 THIRD AVE			ART UNIT	PAPER NUMBER
18TH FLOOR				1637
NEW YORK, NY 10022			MAIL DATE	DELIVERY MODE
			05/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/573,134	Applicant(s) STEINBERG ET AL.
	Examiner MARK STAPLES	Art Unit 1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 02 February 2009.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-7,9 and 11-14 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-7,9 and 11-14 is/are rejected.
 7) Claim(s) 1,7, and 9 is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO/SB/08)
 Paper No(s)/Mail Date 06/15/2006
- 4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____
 5) Notice of Informal Patent Application
 6) Other: _____

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group 1, claims 1-6, 11, and new claims 12-14 in the reply filed on 02/02/2009 is acknowledged. Applicant timely traversed the restriction (election) requirement in the reply filed on 02/02/2009.

The traversal is on the ground(s) that the special technical feature linking the claims is the recited combination of primers of genes for APC, K-ras, β -catenin, **and** B-raf. However claims 1, 7, and 9 recite lists of primers and in the alternative, that is recite "or alternatively" in the lists, and furthermore it is unclear (see 112 claim rejections regarding the lack of clarity in the claims below) as to what "or alternatively" encompasses and it is unclear as to whether this encompasses sequences primers of genes for APC, K-ras, β -catenin, **and** B-raf (thus excluding APC, K-ras, β -catenin, **or** B-raf). However, Applicant's explanation of the claimed invention is accepted and Applicant's argument is thus persuasive to negate the finding of Lack of Unity. Salahshor et al. teach primers of genes for APC, K-ras, and β -catenin but do not specifically teach the B-raf gene. Additionally, it is noted that claims 7 and 9 recite an improper Markush group of: "Primer sequences selected from the group comprising" rather than ". . . the group consisting of" and noting that such language is not present in claim 1. However weighing the explanation and argument of Applicant, it is persuasive that there is no Lack of Unity of Invention and that the election of species is not

required. The finding of Lack of Unity and requirement for election of species are withdrawn.

Claims 1-7, 9, and 11-14 and recited sequences of SEQ ID NOs: 1-18 will be fully examined for patentability.

Priority

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. The papers received are a copy of PCT/DE2004/002161 and a certified copy of German application 103 45 021.1.

Claim Objections

3. Claims 1, 7, and 9 are objected to because of the following informalities: improper grammar in the lists of primers as there is no punctuation as with a comma separating each of the SEQ ID NOs. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-7, 9, and 11-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Art Unit: 1637

6. Claims 1, 7, and 9 recite lists of primers in the alternative, that is recite "or alternatively". It is unclear as to what primers are intended to be in the alternative. Is every primer listed intended to be an alternative, is the prior list of SEQ ID NOs. 1-9 intended to be an alternative with SEQ ID NOs: 10 and 15, or perhaps just SEQ ID NO, 15 intended to be an alternative for APC and if so what other sequence(s) are they intended to be alternatives for, or is some other meaning intended? As independent claims 1, 7, and 9 are unclear, dependent claims 1-7, 9, and 11-13 are also unclear.

7. Claims 1-6 and 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how the cancer is detected as recited in the preamble of claim 1. Although "performing mutational analysis" is recited in the last line of claim 1, it is unclear what results(s) of mutational analysis would qualify as non-invasive early detection of colon cancer or intestinal cancer precursor cells. It is noted that neither the claims nor the specification provide a definition of the mutational analysis needed for the recited detection of colon cancer or intestinal cancer precursor cells.

8. Claims 7 and 9 recite an improper Markush group of: "Primer sequences selected from the group comprising". It is improper to use the term "comprising" instead of "consisting of." Ex parte Dotter, 12 USPQ 382 (Bd. App. 1931). See MPEP § 2173.05(h) I. As independent claim 9 is indefinite, dependent claim 11 is also unclear.

Art Unit: 1637

9. Claim 11 provides for a method of using the kit of claim 9, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where there is no active, positive step(s) delimiting how the method is actually practiced.

The following table is provided for discussion which follows.

Table 1

Sequence matching and Sequences comprising 100% matches to SEQ ID NOS: 1-18

SEQ ID NO: 1

Application 10573134 and
Search Result 20090512_122236_us-10-573-134-1.rng.

Title: US-10-573-134-1
Perfect score: 21
Sequence: 1 ttgcagttatggtaataaccc 21

RESULT 2
ABA78744/c
ID ABA78744 standard; DNA; 121 BP.
XX
AC ABA78744;
XX
DT 24-JAN-2002 (first entry)
XX
DE APC mutation correcting oligonucleotide SEQ ID NO: 1590.
XX
KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;
KW retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;
KW cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBAl; HBA2;
KW adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;
KW haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APCE;
KW mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;
KW familial hypercholesterolemia; UGT1; syndrome; APP; PSEN1; antisense;
KW UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;
KW Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;
KW antilipemic; ss.
XX

Art Unit: 1637

OS Homo sapiens.
XX
PN WO200173002-A2.
XX
PD 04-OCT-2001.
XX
PF 27-MAR-2001; 2001WO-US009761.
XX
PR 27-MAR-2000; 2000US-0192176P.
PR 27-MAR-2000; 2000US-0192179P.
PR 01-JUN-2000; 2000US-0208538P.
PR 30-OCT-2000; 2000US-0244989P.
XX
PA (UYDE) UNIV DELAWARE.
XX
PI Kmiec EB, Gamper HB, Rice MC;
XX
DR WPI; 2001-639230/73.
XX
PT Oligonucleotide for targeted alterations of genetic sequences and for
PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.
XX
PS Claim 7; Page 139; 294pp; English.
XX
CC The present invention provides single-stranded oligonucleotides which
can
CC be used for the targeted alteration of genomic sequences, where the
CC oligonucleotide has at least one mismatch compared with the genomic
CC sequence to be altered. In particular, these sequences are directed at
CC the following genes: adenosine deaminase, p53, beta-globin,
CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus
CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
CC apolipoprotein E (APOE), LDL receptor (LDLR), UDP-
glucuronosyltransferase
CC (UGT1), amyloid precursor protein (APP), presenilin-1 (PSEN1) and
CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
CC such as cancer, adenosine deaminase deficiency, cystic fibrosis,
CC haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
CC Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
CC various syndromes. The present sequence is one of the gene correcting
CC oligonucleotides of the invention
XX
SQ Sequence 121 BP; 32 A; 24 C; 22 G; 43 T; 0 U; 0 Other;

Query Match 100.0%; Score 21; DB 1; Length 121;
Best Local Similarity 100.0%; Pred. No. 3.3;
Matches 21; Conservative 0; Mismatches 0; Indels 0; Gaps
0;

QY 1 TTGCAGTTATGGTCAATACCC 21
||| ||| ||| ||| ||| ||| |||
Db 79 TTGCAGTTATGGTCAATACCC 59

Art Unit: 1637

SEQ ID NO: 2

Application 10573134

Search Result 20090512_122236_us-10-573-134-2.rng.

Title: US-10-573-134-2
Perfect score: 25
Sequence: 1 gtgctctagataaacaggataag 25

RESULT 2
ABA78764
ID ABA78764 standard; DNA; 121 BP.
XX
AC ABA78764;
XX
DT 24-JAN-2002 (first entry)
XX
DE APC mutation correcting oligonucleotide SEQ ID NO: 1610.
XX
KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin; retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V; cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2; adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis; haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE; mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR; familial hypercholesterolaemia; UGTL; syndrome; APP; PSEN1; antisense; UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1; Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic; antilipemic; ss.
XX
OS Homo sapiens.
XX
PN WO200173002-A2.
XX
PD 04-OCT-2001.
XX
PF 27-MAR-2001; 2001WO-US009761.
XX
PR 27-MAR-2000; 2000US-0192176P.
PR 27-MAR-2000; 2000US-0192179P.
PR 01-JUN-2000; 2000US-0208538P.
PR 30-OCT-2000; 2000US-0244989P.
XX
PA (UYDE) UNIV DELAWARE.
XX
PI Kmiec EB, Gamper HB, Rice MC;
XX
DR WPI; 2001-639230/73.
XX
PT Oligonucleotide for targeted alterations of genetic sequences and for
PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.
XX
PS Claim 7; Page 140; 294pp; English.

Art Unit: 1637

XX
 CC The present invention provides single-stranded oligonucleotides which
 can
 CC be used for the targeted alteration of genomic sequences, where the
 CC oligonucleotide has at least one mismatch compared with the genomic
 CC sequence to be altered. In particular, these sequences are directed at
 CC the following genes: adenosine deaminase, p53, beta-globin,
 CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
 CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus
 CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
 CC apolipoprotein E (APOE), LDL receptor (LDLR), UDP-
 glucuronosyltransferase
 CC (UGT1), amyloid precursor protein (APP), presenilin-1 (PSEN1) and
 CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
 CC such as cancer, adenosine deaminase deficiency, cystic fibrosis,
 CC haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
 CC Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
 CC various syndromes. The present sequence is one of the gene correcting
 CC oligonucleotides of the invention
 XX
 SQ Sequence 121 BP; 21 A; 22 C; 21 G; 57 T; 0 U; 0 Other;

Query Match 100.0%; Score 25; DB 1; Length 121;
 Best Local Similarity 100.0%; Pred. No. 0.26;
 Matches 25; Conservative 0; Mismatches 0; Indels 0; Gaps
 0;
 Qy 1 GTGCTCTCAGTATAAACAGGATAAG 25
 |||||||
 Db 15 GTGCTCTCAGTATAAACAGGATAAG 39

SEQ ID NO: 3

Application 10573134

Search Result 20090512_122236_us-10-573-134-3.rng.

Title: US-10-573-134-3
 Perfect score: 20
 Sequence: 1 cctccaaagggtgcacattt 20

RESULT 2
ABA78819
 ID ABA78819 standard; DNA; 121 BP.
 XX
 AC ABA78819;
 XX
 DT 24-JAN-2002 (first entry)
 XX
 DE APC mutation correcting oligonucleotide SEQ ID NO: 1665.
 XX
 KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;
 KW retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;

Art Unit: 1637

KW cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2; adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis; haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE; mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR; familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense; UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1; Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic; antilipemic; ss.
XX
OS Homo sapiens.
XX
PN WO200173002-A2.
XX
PD 04-OCT-2001.
XX
PF 27-MAR-2001; 2001WO-US009761.
XX
PR 27-MAR-2000; 2000US-0192176P.
PR 27-MAR-2000; 2000US-0192179P.
PR 01-JUN-2000; 2000US-0208538P.
PR 30-OCT-2000; 2000US-0244989P.
XX
PA (UYDE) UNIV DELAWARE.
XX
PI Kmiec EB, Gamper HB, Rice MC;
XX
DR WPI: 2001-639230/73.
XX
PT Oligonucleotide for targeted alterations of genetic sequences and for treating cystic fibrosis, comprises at least one mismatch and chemical modification.
XX
PS Claim 7; Page 143; 294pp; English.
XX
CC The present invention provides single-stranded oligonucleotides which can be used for the targeted alteration of genomic sequences, where the oligonucleotide has at least one mismatch compared with the genomic sequence to be altered. In particular, these sequences are directed at the following genes: adenosine deaminase, p53, beta-globin, retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6, apolipoprotein E (APOE), LDL receptor (LDLR), UDP-glucuronosyltransferase (UGT1), amyloid precursor protein (APP), presenilin-1 (PSEN1) and presenilin-2 (PSEN2). These can be used in the gene therapy of diseases such as cancer, adenosine deaminase deficiency, cystic fibrosis, haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia, Alzheimer's disease, melanoma, adenomatous polyposis of the colon and various syndromes. The present sequence is one of the gene correcting oligonucleotides of the invention.
XX
SQ Sequence 121 BP; 41 A; 28 C; 21 G; 31 T; 0 U; 0 Other;

Art Unit: 1637

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Query Match      100.0%;  Score 20;  DB 1;  Length 121;
Best Local Similarity 100.0%;  Pred. No. 10;
Matches 20;  Conservative 0;  Mismatches 0;  Indels 0;  Gaps 0;

Qy      1 CCTCAAAAGGCTGCCACTTG 20
        ||||||| | | | | | | | |
Db      41 CCTCAAAAGGCTGCCACTTG 60

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SEQ ID NO: 4

Application 10573134

Search Result 20090512_122236_us-10-573-134-4.rng.

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Title: US-10-573-134-4
Perfect score: 23
Sequence: i ctgtgacactgtggascttgc 23

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RESULT 3
ABA78855/c
ID  ABA78855 standard; DNA; 121 BP.
XX
AC  ABA78855;
XX
DT  24-JAN-2002 (first entry)
XX
DE  APC mutation correcting oligonucleotide SEQ ID NO: 1701.
XX
KW  Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;
KW  retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;
KW  cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2;
KW  adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;
KW  haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APCE;
KW  mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;
KW  familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense;
KW  UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;
KW  Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;
KW  antilipemic; ss.
XX
OS  Homo sapiens.
XX
PN  WO200173002-A2.
XX
PD  04-OCT-2001.
XX
PF  27-MAR-2001; 2001WO-US009761.
XX
PR  27-MAR-2000; 2000US-0192176P.
PR  27-MAR-2000; 2000US-0192179P.
PR  01-JUN-2000; 2000US-0208538P.
PR  30-OCT-2000; 2000US-0244989P.

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Art Unit: 1637

XX
 PA (UYDE) UNIV DELAWARE.
 XX
 PI Kmiec EB, Gamper HB, Rice MC;
 XX
 DR WPI; 2001-639230/73.
 XX
 PT Oligonucleotide for targeted alterations of genetic sequences and for
 PT treating cystic fibrosis, comprises at least one mismatch and chemical
 PT modification.
 XX
 PS Claim 7; Page 145; 294pp; English.
 XX
 CC The present invention provides single-stranded oligonucleotides which
 can be used for the targeted alteration of genomic sequences, where the
 CC oligonucleotide has at least one mismatch compared with the genomic
 CC sequence to be altered. In particular, these sequences are directed at
 CC the following genes: adenosine deaminase, p53, beta-globin,
 CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
 CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus
 CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
 CC apolipoprotein E (APOE), LDL receptor (LDLR), UDP-
 glucuronosyltransferase
 CC (UGT1), amyloid precursor protein (APP), presenilin-1 (PSEN1) and
 CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
 CC such as cancer, adenosine deaminase deficiency, cystic fibrosis,
 CC haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
 CC Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
 CC various syndromes. The present sequence is one of the gene correcting
 CC oligonucleotides of the invention
 XX
 SQ Sequence 121 BP; 34 A; 30 C; 28 G; 29 T; 0 U; 0 Other;
 Query Match 100.0%; Score 23; DB 1; Length 121;
 Best Local Similarity 100.0%; Pred. No. 2.1;
 Matches 23; Conservative 0; Mismatches 0; Indels 0; Gaps 0;
 Qy 1 CTGTGACACTGCTGGAACCTTCGC 23
 |||||||
 Db 33 CTGTGACACTGCTGGAACCTTCGC 11

SEQ ID NO: 5

Application 10573134
Search Result 20090512_122236_us-10-573-134-5.mg

Title: US-10-573-134-5
Perfect score: 25
Sequence: 1 agcacccctagaaccggatccagcg 25

Art Unit: 1637

RESULT 3
ABA78859
ID ABA78859 standard; DNA; 121 BP.
XX
AC ABA78859;
XX
DT 24-JAN-2002 (first entry)
XX
DE APC mutation correcting oligonucleotide SEQ ID NO: 1705.
XX
KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin; retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V; cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2; adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis; haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE; mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR; familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense; UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1; Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic; antilipemic; ss.
XX
OS Homo sapiens.
XX
PN WO200173002-A2.
XX
PD 04-OCT-2001.
XX
PF 27-MAR-2001; 2001WO-US009761.
XX
PR 27-MAR-2000; 2000US-0192176P.
PR 27-MAR-2000; 2000US-0192179P.
PR 01-JUN-2000; 2000US-0208538P.
PR 30-OCT-2000; 2000US-0244989P.
XX
PA (UYDE) UNIV DELAWARE.
XX
PI Kmiec EB, Gamper HB, Rice MC;
XX
DR WPI; 2001-639230/73.
XX
PT Oligonucleotide for targeted alterations of genetic sequences and for
PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.
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PS Claim 7; Page 145; 294pp; English.
XX
CC The present invention provides single-stranded oligonucleotides which
can
CC be used for the targeted alteration of genomic sequences, where the
CC oligonucleotide has at least one mismatch compared with the genomic
CC sequence to be altered. In particular, these sequences are directed at
CC the following genes: adenosine deaminase, p53, beta-globin,
CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus

Art Unit: 1637

CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
 CC apolipoprotein E (APOE), LDL receptor (LDLR), UDP-
 glucuronosyltransferase
 CC (UGT1), amyloid precursor protein (APP), presenilin-1 (PSEN1) and
 CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
 CC such as cancer, adenosine deaminase deficiency, cystic fibrosis,
 CC haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
 CC Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
 CC various syndromes. The present sequence is one of the gene correcting
 CC oligonucleotides of the invention
 XX

SQ Sequence 121 BP; 35 A; 33 C; 24 G; 29 T; 0 U; 0 Other;

Query Match 100.0%; Score 25; DB 1; Length 121;
 Best Local Similarity 100.0%; Pred. No. 0.34;
 Matches 25; Conservative 0; Mismatches 0; Indels 0; Gaps
 0;

Qy 1 AGCACCTAGAACCAAATCCAGCAG 25
 |||||||
 Db 19 AGCACCTAGAACCAAATCCAGCAG 43

SEQ ID NO: 6

Application 10573134 and
 Search Result 20090512_122236_us-10-573-134-6.rng.

Title: US-10-573-134-6
 Perfect score: 20
 Sequence: tggcatggtttgtccaggc 20

RESULT 2
 AAF62230/c
 ID AAF62230 standard; DNA; 37 BP.
 XX
 AC AAF62230;
 XX
 DT 21-MAY-2001 (first entry)
 XX
 DE Probe for human apcl (adenomatous polyposis coli) gene.
 XX
 KW Human; detection; cancer; pre-cancer; foetal abnormality; apoptosis;
 colon cancer; probe; adenomatous polyposis coli; apc; ss.
 XX
 OS Homo sapiens.
 XX
 PN WO200118252-A2.
 XX
 PD 15-MAR-2001.
 XX
 PF 08-SEP-2000; 2000WO-US024639.
 XX

Art Unit: 1637

PR 08-SEP-1999; 99US-0152847P.
PR 07-DEC-1999; 99US-00455950.
XX
PA (EXAC-) EXACT LAB INC.
XX
PI Shuber AP;
XX
DR WPI; 2001-235215/24.
XX
PT Detecting a disease (e.g. cancer or pre-cancer), determining its status,
PT or screening a patient for a disease, comprises determining the
integrity
PT of nucleic acids in a patient sample containing shed cells or cellular
PT debris.
XX
PS Example 3; Page 20; 44pp; English.
XX
CC A method for determining the disease status of a patient or screening a
CC patient for disease, comprises determining the integrity of nucleic
acids
CC in a sample containing cells which have been shed or cellular debris.
The
CC method is useful for detecting a disease, determining the disease status
CC of a patient or screening a patient for a disease. The disease may be
CC cancer (e.g. colon cancer, lung cancer, oesophageal cancer, prostate
CC cancer, stomach cancer, pancreatic cancer, liver cancer or lymphoma) or
CC pre-cancer. The methods are also useful for assessing the integrity of
CC DNA in a biological sample or for assessing foetal abnormalities. The
CC methods are also useful as assays for apoptosis. The present sequence
CC represents a probe for human apc1 (adenomatous polyposis coli) DNA,
which
CC is used in an example illustrating the use of the method for the
CC detection of colon cancer
XX
SQ Sequence 37 BP; 14 A; 12 C; 8 G; 3 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 1; Length 37;
Best Local Similarity 100.0%; Pred. No. 9.4;
Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 TGGCATGGTTGTCCAGGGC 20
|||...|||...|||...|||...|||
Db 26 TGGCATGGTTGTCCAGGGC 7

SEQ ID NO: 7

Application 10573134 and
Search Result 20090512_122236_us-10-573-134-7.rng.
Title: US-10-573-134-7
Perfect score: 22
Sequence: 1 acaaaccatgccaccaaggaga 22

Art Unit: 1637

RESULT 2
AAF62230
ID AAF62230 standard; DNA; 37 BP.
XX
AC AAF62230;
XX
DT 21-MAY-2001 (first entry)
XX
DE Probe for human apcl (adenomatous polyposis coli) gene.
XX
KW Human; detection; cancer; pre-cancer; foetal abnormality; apoptosis;
colon cancer; probe; adenomatous polyposis coli; apc; ss.
XX
OS Homo sapiens.
XX
PN WO200118252-A2.
XX
PD 15-MAR-2001.
XX
PF 08-SEP-2000; 2000WO-US024639.
XX
PR 08-SEP-1999; 99US-0152847P.
PR 07-DEC-1999; 99US-00455950.
XX
PA (EXAC-) EXACT LAB INC.
XX
PI Shuber AP;
XX
DR WPI; 2001-235215/24.
XX
PT Detecting a disease (e.g. cancer or pre-cancer), determining its status,
PT or screening a patient for a disease, comprises determining the
integrity
PT of nucleic acids in a patient sample containing shed cells or cellular
PT debris.
XX
PS Example 3; Page 20; 44pp; English.
XX
CC A method for determining the disease status of a patient or screening a
CC patient for disease, comprises determining the integrity of nucleic
acids
CC in a sample containing cells which have been shed or cellular debris.
The
CC method is useful for detecting a disease, determining the disease status
CC of a patient or screening a patient for a disease. The disease may be
CC cancer (e.g. colon cancer, lung cancer, oesophageal cancer, prostate
CC cancer, stomach cancer, pancreatic cancer, liver cancer or lymphoma) or
CC pre-cancer. The methods are also useful for assessing the integrity of
CC DNA in a biological sample or for assessing foetal abnormalities. The
CC methods are also useful as assays for apoptosis. The present sequence
CC represents a probe for human apcl (adenomatous polyposis coli) DNA,
which
CC is used in an example illustrating the use of the method for the
CC detection of colon cancer

Art Unit: 1637

XX
SQ Sequence 37 BP; 14 A; 12 C; 8 G; 3 T; 0 U; 0 Other;

Query Match 100.0%; Score 22; DB 1; Length 37;
Best Local Similarity 100.0%; Pred. No. 5.7;
Matches 22; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 ACAAAACCATGCCACCAAGCAGA 22
|||||||||||||||||||||||
Db 14 ACAAAACCATGCCACCAAGCAGA 35

SEQ ID NO: 8

Application 10573134 and
Search Result 20090512_122236_us-10-573-134-8.rng.

Title: US-10-573-134-8
Perfect score: 24
Sequence: 1 gagcactcaggctggatgaacaag 24

RESULT 2
ABA78900
ID ABA78900 standard; DNA; 121 BP.
XX
AC ABA78900;
XX
DT 24-JAN-2002 (first entry)
XX
DE APC mutation correcting oligonucleotide SEQ ID NO: 1746.
XX
KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;
KW retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;
KW cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2;
KW adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;
KW haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE;
KW mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;
KW familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense;
KW UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;
KW Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;
KW antilipemic; ss.
XX
OS Homo sapiens.
XX
PN WO200173002-A2.
XX
PD 04-OCT-2001.
XX
PF 27-MAR-2001; 2001WO-US009761.
XX
PR 27-MAR-2000; 2000US-0192176P.

Art Unit: 1637

PR 27-MAR-2000; 2000US-0192179P.
PR 01-JUN-2000; 2000US-0208538P.
PR 30-OCT-2000; 2000US-0244989P.
XX
PA (UYDE) UNIV DELAWARE.
XX
PI Kmiec EB, Gamper HB, Rice MC;
XX
DR WPI; 2001-639230/73.
XX
PT Oligonucleotide for targeted alterations of genetic sequences and for
PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.
XX
PS Claim 7; Page 147; 294pp; English.
XX
CC The present invention provides single-stranded oligonucleotides which
can
be used for the targeted alteration of genomic sequences, where the
oligonucleotide has at least one mismatch compared with the genomic
sequence to be altered. In particular, these sequences are directed at
the following genes: adenosine deaminase, p53, beta-globin,
retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
(CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus
1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
apolipoprotein E (APOE), LDL receptor (LDLR), UDP-
glucuronosyltransferase
CC (UGT1), amyloid precursor protein (APP), presenilin-1 (PSEN1) and
CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
such as cancer, adenosine deaminase deficiency, cystic fibrosis,
haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
various syndromes. The present sequence is one of the gene correcting
oligonucleotides of the invention
XX
SQ Sequence 121 BP; 38 A; 26 C; 24 G; 33 T; 0 U; 0 Other;

Query Match 100.0%; Score 24; DB 1; Length 121;
Best Local Similarity 100.0%; Pred. No. 0.79;
Matches 24; Conservative 0; Mismatches 0; Indels 0; Gaps
0;

Qy 1 GAGCACTCAGGCTGGATGAAACAAG 24
Db 44 GAGCACTCAGGCTGGATGAAACAAG 67

SEQ ID NO: 9

Application 10573134 and
Search Result 20090512_122236_us-10-573-134-9.rng.

Art Unit: 1637

Title: US-10-573-134-9
Perfect score: 20
Sequence: 1 ttccagatgctgatacttta 20

RESULT 10
AAA93450
ID AAA93450 standard; cDNA; 8229 BP.
XX
AC AAA93450;
XX
DT 16-JAN-2001 (first entry)
XX
DE Human APC (DP2.5) cDNA (splice variant 2).
XX
KW APC gene; Adenomatous Polyposis Coli gene; human; chromosome 5q21;
KW familial adenomatous polyposis; FAP locus; Gardner's syndrome; GS;
KW sporadic tumour; adenoma; carcinoma; cancer; lung; breast; colon;
rectum;
KW bladder; liver; sarcoma; stomach; prostate; leukaemia; lymphoma;
KW tumour suppressor; anti-APC antibody; detection; diagnosis; prognosis;
KW genetic predisposition; drug screening; DP2.5; splice variant; ds.
XX
OS Homo sapiens.
XX
PN US6114124-A.
XX
PD 05-SEP-2000.
XX
PF 25-MAY-1995; 95US-00450582.
XX
PR 16-JAN-1991; 91GB-00000962.
PR 16-JAN-1991; 91GB-00000963.
PR 16-JAN-1991; 91GB-00000974.
PR 16-JAN-1991; 91GB-00000975.
PR 08-AUG-1991; 91US-00741940.
PR 12-AUG-1994; 94US-00289548.
XX
PA (ICIL) IMPERIAL CHEM IND PLC.
PA (UYJO) UNIV JOHNS HOPKINS.
PA (UTAH) UNIV UTAH.
PA (CANC-) CANCER INST.
XX
PI Carlson M, Groden J, Joslyn G, Kinzler K, Markham AF, Anand R;
PI Albertsen H, White RL, Thliveris A, Nakamura Y, Vogelstein B;
PI Hedge PJ;
XX
DR WPI; 2000-565003/52.
DR P-PSDB; AAB23012.
XX
PT Detecting Adenomatous Polyposis Coli (APC) protein in a sample for
PT diagnosing cancers, involves contacting the sample with antibodies that
PT specifically bind to APC protein and detecting the complex formed.
XX

Art Unit: 1637

PS Example 7; Fig 7A1-7W; 125pp; English.
 XX
 CC The invention relates to a novel method for detecting Adenomatous
 CC Polyposis Coli (APC) protein in a sample. The method involves contacting
 CC the sample with antibodies which specifically binds to the 2843 amino
 CC acid form of the human APC protein, or to a mutant APC protein, and
 CC detecting an APC-antibody complex. Mutations in the APC gene play a role
 CC in tumorigenesis, indicating that it is a tumour suppressor gene. It is
 CC located on chromosome 5q21, which corresponds to the FAP (familial
 CC adenomatous polyposis) locus. FAP is an autosomal dominant inherited
 CC disease in which affected individuals develop hundreds to thousands of
 CC adenomatous polyps in the colon and rectum, some of which progress to
 CC malignancy. The FAP locus is often found to be deleted in sporadic
 (i.e.,
 CC non-familial) adenomas and carcinomas, and chromosome 5q deletions have
 CC also been observed in tumours of the lung, breast, colon, rectum,
 CC bladder, liver, sarcomas, stomach, and prostate, and in leukaemias and
 CC lymphomas. Although the FAP locus contains several other genes such as
 CC FER, TB1, TB2, and MCC, it is thought that mutations in the APC gene
 play
 CC a key role in the development of FAP and sporadic tumours. The method is
 CC useful for detecting APC protein and its mutant forms in foetal tissue,
 CC placental tissue, amniotic fluid, blood, serum or a tumour sample. The
 CC method is useful for diagnosing or prognosing neoplastic tissue, for
 CC detecting a genetic predisposition to cancer, for detecting germline and
 CC somatic alteration of wild-type APC genes, and for testing therapeutic
 CC agents for the ability to suppress tumours. The present sequence
 CC represents cDNA encoding a 2742 amino acid splice variant of the human
 CC APC protein
 XX
 SQ Sequence 8229 BP; 2863 A; 1702 C; 1670 G; 1994 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 1; Length 8229;
 Best Local Similarity 100.0%; Pred. No. 32;
 Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps
 0;

Qy 1 TTCCAGATGCTGATACTTTA 20
 ||||||| ||||| ||||| |||||
 Db 4142 TTCCAGATGCTGATACTTTA 4161

SEQ ID NO: 10

Application 10573134 and
 Search Result 20090310_113718_us-10-573-134-10.rng.

Title: US-10-573-134-10
 Perfect score: 20
 Sequence: 1 ctgaatcatctaataagggtcc 20

Art Unit: 1637

RESULT 7
ABA78911/c
ID ABA78911 standard; DNA; 121 BP.
XX
AC ABA78911;
XX
DT 24-JAN-2002 (first entry)
XX
DE APC mutation correcting oligonucleotide SEQ ID NO: 1757.
XX
KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;
KW retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;
KW cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2;
KW adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;
KW haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE;
KW mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;
KW familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense;
KW UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;
KW Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;
KW antilipemic; ss.
XX
OS Homo sapiens.
XX
PN WO200173002-A2.
XX
PD 04-OCT-2001.
XX
PF 27-MAR-2001; 2001WO-US009761.
XX
PR 27-MAR-2000; 2000US-0192176P.
PR 27-MAR-2000; 2000US-0192179P.
PR 01-JUN-2000; 2000US-0208538P.
PR 30-OCT-2000; 2000US-0244989P.
XX
PA (UYDE) UNIV DELAWARE.
XX
PI Kmiec EB, Gamper HB, Rice MC;
XX
DR WPI; 2001-639230/73.
XX
PT Oligonucleotide for targeted alterations of genetic sequences and for
PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.
XX
PS Claim 7; Page 147; 294pp; English.
XX
CC The present invention provides single-stranded oligonucleotides which
can
CC be used for the targeted alteration of genomic sequences, where the
CC oligonucleotide has at least one mismatch compared with the genomic
CC sequence to be altered. In particular, these sequences are directed at
CC the following genes: adenosine deaminase, p53, beta-globin,
CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus

Art Unit: 1637

CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
 CC apolipoprotein E (APOE), LDL receptor (LDLR), UDP-
 glucuronosyltransferase
 CC (UGT1), amyloid precursor protein (APP), presenilin-1 (PSEN1) and
 CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
 CC such as cancer, adenosine deaminase deficiency, cystic fibrosis,
 CC haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
 CC Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
 CC various syndromes. The present sequence is one of the gene correcting
 CC oligonucleotides of the invention
 XX

SQ Sequence 121 BP; 52 A; 16 C; 23 G; 30 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 1; Length 121;
 Best Local Similarity 100.0%; Pred. No. 11;
 Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 CTGAATCATCTAATAAGGTCC 20
 |||||||
 Db 63 CTGAATCATCTAATAAGGTCC 44

SEQ ID NO: 11

Application 10573134 and
 Search Result 20090512_122350_us-10-573-134-11.rng.

Title: US-10-573-134-11
 Perfect score: 21
 Sequence: 1 ctgttgagatatttgatagtg 21

RESULT 7
 AAX00191
 ID AAX00191 standard; DNA; 32 BP.
 XX
 AC AAX00191;
 XX
 DT 23-MAR-1999 (first entry)
 XX
 DE K-ras mutation detection common PCR forward primer.
 XX
 KW K-ras; mutation; detection; PCR primer; diagnosis; cancer; human;
 KW colorectal cancer; non-small cell lung cancer; pancreatic cancer; ss.
 XX
 OS Synthetic.
 OS Homo sapiens.
 XX
 PN GB2327497-A.
 XX
 PD 27-JAN-1999.
 XX

Art Unit: 1637

PF 15-JUL-1998; 98GB-00015224.
XX
PR 18-JUL-1997; 97GB-00015034.
XX
PA (ZENECA LTD.
XX
PI Ferrie RM, Ellison G, Callaghan K, Fox JC;
XX
DR WPI; 1999-073586/07.
XX
PT Diagnostic method for K-ras mutation in cancer - by contacting nucleic acid sample with new diagnostic primer, nucleotide triphosphate(s) and polymerisation agent and detecting extension product.
XX
PS Example 1; Page 6; 58pp; English.
XX
CC A diagnostic method has been developed for the detection of K-ras mutations in cancer. The method comprises: (i) contacting a test sample of nucleic acid with a diagnostic primer for a K-ras mutation in the presence of nucleotide triphosphates and an agent for polymerisation such that the diagnostic primer is extended only when a K-ras mutation is present in the sample; and (ii) detecting the extension product formed. The method is used for detection of cancer, particularly colorectal cancer, non-small cell lung cancer and pancreatic cancer. The method gives lower numbers of false positives and false negatives than the prior art and is less invasive for the patient. As the procedure does not require use of a hospital suite, it is much cheaper and poses less risk to the patient from anaesthesia and procedural complications. The present sequence represents a primer which is used in an example from the present invention
XX
SQ Sequence 32 BP; 8 A; 3 C; 9 G; 12 T; 0 U; 0 Other;

Query Match 100.0%; Score 21; DB 1; Length 32;
Best Local Similarity 100.0%; Pred. No. 12;
Matches 21; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 CTGGTGGAGTATTTGATAGTG 21
Db 4 CTGGTGGAGTATTTGATAGTG 24

SEQ ID NO: 12

Application 10573134 and
Search Result 20090512_122350_us-10-573-134-12.rng.

Art Unit: 1637

Title: US-10-573-134-12
Perfect score: 21
Sequence: 1 tctattgttggatcatatccg 21

RESULT 3
AAX00201
ID AAX00201 standard; DNA; 27 BP.
XX
AC AAX00201;
XX
DT 23-MAR-1999 (first entry)
XX
DE K-ras exon I PCR reverse primer #1.
XX
KW K-ras; mutation; detection; PCR primer; diagnosis; cancer; human;
KW colorectal cancer; non-small cell lung cancer; pancreatic cancer; ss.
XX
OS Synthetic.
OS Homo sapiens.
XX
PN GB2327497-A.
XX
PD 27-JAN-1999.
XX
PF 15-JUL-1998; 98GB-00015224.
XX
PR 18-JUL-1997; 97GB-00015034.
XX
PA (ZENE) ZENECA LTD.
XX
PI Ferrie RM, Ellison G, Callaghan K, Fox JC;
XX
DR WPI; 1999-073586/07.
XX
PT Diagnostic method for K-ras mutation in cancer - by contacting nucleic acid sample with new diagnostic primer, nucleotide triphosphate(s) and polymerisation agent and detecting extension product.
XX
PS Example 2; Page 25; 58pp; English.
XX
CC A diagnostic method has been developed for the detection of K-ras mutations in cancer. The method comprises: (i) contacting a test sample of nucleic acid with a diagnostic primer for a K-ras mutation in the presence of nucleotide triphosphates and an agent for polymerisation such that the diagnostic primer is extended only when a K-ras mutation is present in the sample; and (ii) detecting the extension product formed. The method is used for detection of cancer, particularly colorectal cancer, non-small cell lung cancer and pancreatic cancer. The method gives lower numbers of false positives and false negatives than the prior art and is less invasive for the patient. As the procedure does not require use of a hospital suite, it is much cheaper and poses less risk

Art Unit: 1637

CC to the patient from anaesthesia and procedural complications. The present
 CC sequence represents a primer which is used in an example from the present
 CC invention
 XX
 SQ Sequence 27 BP; 5 A; 7 C; 4 G; 11 T; 0 U; 0 Other;

Query Match 100.0%; Score 21; DB 1; Length 27;
 Best Local Similarity 100.0%; Pred. No. 13;
 Matches 21; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 TCTATTGTTGGATCATATTCTG 21
 |||||||
 Db 3 TCTATTGTTGGATCATATTCTG 23

SEQ ID NO: 13

Coste et al. (1998)

See β -catenin primer PH2 in the 2nd paragraph on p. 8846 and given below:

Qy 1 CTGATTTGATGGAGTTGGAC 20
 |||||||
 PH2, 5' CTGATTTGATGGAGTTGGAC - 3'

SEQ ID NO: 14

CTTGAGTGAAGGACTGAGAA

The reverse complement is:

TTCTCAGTCCTTCACTCAAG

Which is taught by Nollet et al. (1996) who are referenced by Coste et al.(see reference no. 40)

Nollet et al. teach the reverse complement sequence in the β -catenin sequence on p. 416 as given below.

Qy 1 TTCTCAGTCCTTCACTCAAG 20
 |||||||
 424 TTCTCAGTCCTTCACTCAAG 443

Not also that Coste et al. teach the first 8 base sequence of SEQ ID NO: 14 as the last 8 base bolded sequence in primer PH1 in the 2nd paragraph on p. 8846 and given below:PH1, 5'-TACAGCTACTTGT**TCTTGAGTG**-3'

Art Unit: 1637

SEQ ID NO: 15

Application 10573134 and
Search Result 20090512_122350_us-10-573-134-15.rng.

Title: US-10-573-134-15
Perfect score: 19
Sequence: 1 gaatcagctccatccaagt 19

RESULT 11
AAA93450
ID AAA93450 standard; cDNA; 8229 BP.
XX
AC AAA93450;
XX
DT 16-JAN-2001 (first entry)
XX
DE Human APC (DP2.5) cDNA (splice variant 2).
XX
KW APC gene; Adenomatous Polyposis Coli gene; human; chromosome 5q21;
KW familial adenomatous polyposis; FAP locus; Gardner's syndrome; GS;
KW sporadic tumour; adenoma; carcinoma; cancer; lung; breast; colon;
rectum;
KW bladder; liver; sarcoma; stomach; prostate; leukaemia; lymphoma;
KW tumour suppressor; anti-APC antibody; detection; diagnosis; prognosis;
KW genetic predisposition; drug screening; DP2.5; splice variant; ds.
XX
OS Homo sapiens.
XX
PN US6114124-A.
XX
PD 05-SEP-2000.
XX
PF 25-MAY-1995; 95US-00450582.
XX
PR 16-JAN-1991; 91GB-00000962.
PR 16-JAN-1991; 91GB-00000963.
PR 16-JAN-1991; 91GB-00000974.
PR 16-JAN-1991; 91GB-00000975.
PR 08-AUG-1994; 91US-00741940.
PR 12-AUG-1994; 94US-00289548.
XX
PA (ICIL) IMPERIAL CHEM IND PLC.
PA (UYJO) UNIV JOHNS HOPKINS.
PA (UTAH) UNIV UTAH.
PA (CANC-) CANCER INST.
XX
PI Carlson M, Groden J, Joslyn G, Kinzler K, Markham AF, Anand R;
PI Albertsen H, White RL, Thliveris A, Nakamura Y, Vogelstein B;
PI Hedge PJ;
XX
DR WPI; 2000-565003/52.

Art Unit: 1637

DR P-PSDB; AAB23012.
XX
PT Detecting Adenomatous Polyposis Coli (APC) protein in a sample for
PT diagnosing cancers, involves contacting the sample with antibodies that
PT specifically bind to APC protein and detecting the complex formed.
XX
PS Example 7; Fig 7A1-7W; 125pp; English.
XX
CC The invention relates to a novel method for detecting Adenomatous
CC Polyposis Coli (APC) protein in a sample. The method involves contacting
CC the sample with antibodies which specifically binds to the 2843 amino
CC acid form of the human APC protein, or to a mutant APC protein, and
CC detecting an APC-antibody complex. Mutations in the APC gene play a role
CC in tumorigenesis, indicating that it is a tumour suppressor gene. It is
CC located on chromosome 5q21, which corresponds to the FAP (familial
CC adenomatous polyposis) locus. FAP is an autosomal dominant inherited
CC disease in which affected individuals develop hundreds to thousands of
CC adenomatous polyps in the colon and rectum, some of which progress to
CC malignancy. The FAP locus is often found to be deleted in sporadic
(i.e.,
CC non-familial) adenomas and carcinomas, and chromosome 5q deletions have
CC also been observed in tumours of the lung, breast, colon, rectum,
CC bladder, liver, sarcomas, stomach, and prostate, and in leukaemias and
CC lymphomas. Although the FAP locus contains several other genes such as
CC FER, TB1, TB2, and MCC, it is thought that mutations in the APC gene
play
CC a key role in the development of FAP and sporadic tumours. The method is
CC useful for detecting APC protein and its mutant forms in foetal tissue,
CC placental tissue, amniotic fluid, blood, serum or a tumour sample. The
CC method is useful for diagnosing or prognosing neoplastic tissue, for
CC detecting a genetic predisposition to cancer, for detecting germline and
CC somatic alteration of wild-type APC genes, and for testing therapeutic
CC agents for the ability to suppress tumours. The present sequence
CC represents cDNA encoding a 2742 amino acid splice variant of the human
CC APC protein
XX
SQ Sequence 8229 BP; 2863 A; 1702 C; 1670 G; 1994 T; 0 U; 0 Other;

Query Match 100.0%; Score 19; DB 1; Length 8229;
Best Local Similarity 100.0%; Pred. No. 83;
Matches 19; Conservative 0; Mismatches 0; Indels 0; Gaps
0;

QY 1 GAATCAGCTCCATCCAAGT 19
||||||| ||||| ||||| |||||
Db 3381 GAATCAGCTCCATCCAAGT 3399

SEQ ID NO: 16

Application 10573134 and
Search Result 20090512_122350_us-10-573-134-16.rng.

Art Unit: 1637

Title: US-10-573-134-16
Perfect score: 19
Sequence: 1 ttcttgctattgcagggt 19

RESULT 12
ABA78836
ID ABA78836 standard; DNA; 121 BP.
XX
AC ABA78836;
XX
DT 24-JAN-2002 (first entry)
XX
DE APC mutation correcting oligonucleotide SEQ ID NO: 1682.
XX
KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;
KW retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;
KW cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2;
KW adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;
KW haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE;
KW mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;
KW familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense;
KW UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;
KW Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;
KW antilipemic; ss.
XX
OS Homo sapiens.
XX
PN WO200173002-A2.
XX
PD 04-OCT-2001.
XX
PF 27-MAR-2001; 2001WO-US009761.
XX
PR 27-MAR-2000; 2000US-0192176P.
PR 27-MAR-2000; 2000US-0192179P.
PR 01-JUN-2000; 2000US-0208538P.
PR 30-OCT-2000; 2000US-0244989P.
XX
PA (UYDE) UNIV DELAWARE.
XX
PI Kmiec EB, Gamper HB, Rice MC;
XX
DR WPI; 2001-639230/73.
XX
PT Oligonucleotide for targeted alterations of genetic sequences and for
PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.
XX
PS Claim 7; Page 144; 294pp; English.
XX
CC The present invention provides single-stranded oligonucleotides which
can
CC be used for the targeted alteration of genomic sequences, where the
CC oligonucleotide has at least one mismatch compared with the genomic

Art Unit: 1637

CC sequence to be altered. In particular, these sequences are directed at
 CC the following genes: adenosine deaminase, p53, beta-globin,
 CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
 CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus
 CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
 CC apolipoprotein E (APOE), LDL receptor (LDLR), UDP-
 glucuronosyltransferase
 CC (UGT1), amyloid precursor protein (APP), presenilin-1 (PSEN1) and
 CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
 CC such as cancer, adenosine deaminase deficiency, cystic fibrosis,
 CC haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
 CC Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
 CC various syndromes. The present sequence is one of the gene correcting
 CC oligonucleotides of the invention

XX

SQ Sequence 121 BP; 30 A; 24 C; 19 G; 48 T; 0 U; 0 Other;

Query Match 100.0%; Score 19; DB 1; Length 121;
 Best Local Similarity 100.0%; Pred. No. 28;
 Matches 19; Conservative 0; Mismatches 0; Indels 0; Gaps
 0;

Qy 1 TTTCTGCTATTCAGGGT 19
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 Db 22 TTTCTGCTATTCAGGGT 40

SEQ ID NO: 17

Application 10573134 and
 Search Result 20090512_122350_us-10-573-134-17.rng.

Title: US-10-573-134-17
 Perfect score: 20
 Sequence: 1 tgtatcaccatctccatatac 20

RESULT 5
HUMBRAFA
 LOCUS HUMBRAFA 987 bp mRNA linear PRI 09-APR-1996
 DEFINITION Human B-raf oncogene mRNA, 3' end.
 ACCESSION M21001
 VERSION M21001.1 GI:179534
 KEYWORDS B-raf oncogene; raf oncogene.
 SOURCE Homo sapiens (human)
 ORGANISM Homo sapiens
 Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
 Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
 Catarrhini; Hominidae; Homo.
 REFERENCE 1 (bases 1 to 987)
 AUTHORS Ikawa,S., Fukui,M., Ueyama,Y., Tamaoki,N., Yamamoto,T. and
 Toyoshima,K.
 TITLE B-raf, a new member of the raf family, is activated by DNA
 rearrangement

Art Unit: 1637

JOURNAL Mol. Cell. Biol. 8 (6), 2651-2654 (1988)
 PUBMED 3043188
 COMMENT Original source text: Human cDNA to mRNA.
 FEATURES Location/Qualifiers
 source 1. .987
 /organism="Homo sapiens"
 /mol_type="mRNA"
 /db_xref="taxon:9606"
 /clone="lambda-EBR[1,2]"
 CDS <1. .987
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 Best Local Similarity 100.0%; Pred. No. 43;
 Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;
 Qy 1 TGTATCACCCTCTCCATATC 20
 |||||||
 Db 296 TGTATCACCCTCTCCATATC 315

SEQ ID NO: 18

Application 10573134 and
 Search Result 20090512_122350_us-10-573-134-18.rng.

Title: US-10-573-134-18
 Perfect score: 20
 Sequence: 1 gcattctgtatgactcttgt 20

RESULT 5
 HUMBRAFA/c
 LOCUS HUMBRAFA 987 bp mRNA linear PRI 09-APR-1996
 DEFINITION Human B-raf oncogene mRNA, 3' end.
 ACCESSION M21001
 VERSION M21001.1 GI:179534

Art Unit: 1637

KEYWORDS B-raf oncogene; raf oncogene.

SOURCE Homo sapiens (human)

ORGANISM Homo sapiens

Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo.

REFERENCE 1 (bases 1 to 987)

AUTHORS Ikawa,S., Fukui,M., Ueyama,Y., Tamaoki,N., Yamamoto,T. and Toyoshima,K.

TITLE B-raf, a new member of the raf family, is activated by DNA rearrangement

JOURNAL Mol. Cell. Biol. 8 (6), 2651-2654 (1988)

PUBMED 3043188

COMMENT Original source text: Human cDNA to mRNA.

FEATURES Location/Qualifiers

source 1..987
 /organism="Homo sapiens"
 /mol_type="mRNA"
 /db_xref="taxon:9606"
 /clone="lambda-EBR[1,2]"

CDS <1..987
 /codon_start=1
 /product="B-raf protein"
 /protein_id="AAA96495.1"
 /db_xref="GI:179535"

/translation="KTLGRRDSSDDWEIPDGQITVGQRIGSGSFGTVYKGKWHGDVAV
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 LHIIETKFEMIKLIDIAQTAQGMDYLHAKSIIHDLKSNNIFLHEDLTVKIGDFGLA
 TVKSRWSGSHQFEQLSGSILWMAPEVIRMQDKNPYSFQSDVYAFGIVLYELMTGQLPY
 SNIINNRDQIIFMVGRGYLSPDLSKVRSNCPKAMKRLMAECLKKRDERPLFPQILASI
 ELLARSLPKIHRSAEPLNRAGFQTEDFSLYACASPKTIQAGGGYGAFTPVD"

ORIGIN

Query Match 100.0%; Score 20; DB 5; Length 987;
 Best Local Similarity 100.0%; Pred. No. 7;
 Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

QY 1 GCATTCTGATGACTTCTGGT 20
 ||||||| ||||| ||||| |||||
 Db 568 GCATTCTGATGACTTCTGGT 549

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 7, 9, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kmiec et al. (WO200173002 published 2001) and Buck et al. (1999).

As claims 7 and 9 recite primers selected from a group of primers, these claims are rejected over prior art teaching at least two of the primers as follows.

Claims 7, 9, and 11 are rejected for SEQ ID NOs: 1-5, 8, 10, and 16, as described following. Kmiec et al. disclose amplification of DNA in the APC gene with primers designed for amplification of detection of cancer including colon cancer (see

Table 1 above).

Further regarding claims 9 and 11, Kmiec et al. teach a kit comprising oligonucleotides (see claim 24). Further regarding claim 11, this claim recites an intended use of the kit of claim 9 to be used in a method for detection of colon cancer or colon cancer precursor cells. While this intended use carries no patentable weight, Kmiec et al. teach use of primer sequences for the detection of colon cancer (as given in Table 1 above and see Also Example 11 beginning on p. 131).

Kmiec et al. expressly disclose the identical nucleic acid sequence presented in SEQ ID NO: 1-5, 8, 10, and 16 of the instant disclosure. It is noted that the instant primer sites of SEQ ID NOs: 1-5, 8, 10, and 16 are contained within the sequence disclosed by Kmiec et al.

The above described reference does not specifically disclose the identical primer sequences of SEQ ID NOs: 1-5, 8, 10, and 16, respectively, used in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated, "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the APC gene and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

13. Claims 7, 9, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (WO200118252 published 2001), Buck et al. (1999), and Stratagene (1988 catalog).

As claims 7 and 9 recite primers selected from a group of primers, these claims are rejected over prior art teaching at least two of the primers as follows.

Claims 7, 9, and 11 are rejected for SEQ ID NOs: 6 and 7, as described following. Shuber et al. disclose amplification of DNA in the APC gene with primers designed for amplification of detection of cancer including colon cancer (see Table 1 above).

Regarding claims 9 and 11, Shuber et al do not specifically teach a kit.

Shuber et al. expressly disclose the identical nucleic acid sequence presented in SEQ ID NO: 6 and 7 of the instant disclosure. It is noted that the instant primer sites of SEQ ID NOs: 6 and 7 are contained within the sequence disclosed by Shuber et al.

The above described reference does not specifically disclose the identical primer sequences of SEQ ID NOs: 6 and 7, respectively, used in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious.

Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try

to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the APC gene and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all

possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Regarding claim 9 and 11, Stratagene catalog teaches a motivation to combine reagents into kit format (page 39). It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the primers of Shuber et al. and Buck et al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

14. Claims 7, 9, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferrie et al. (GB2327497 published 1999) and Buck et al. (1999).

As claims 7 and 9 recite primers selected from a group of primers, these claims are rejected over prior art teaching at least two of the primers as follows.

Claims 7, 9, and 11 are rejected for SEQ ID NOs: 11 and 12, as described following. Ferrie et al. disclose amplification of DNA in the K-ras gene with primers designed for amplification of detection of cancer including colon cancer (see Table 1 above).

Further regarding claims 9 and 11, Ferrie et al. teach a kit comprising primers (see Abstract and claim 8 and 9). Further regarding claim 11, this claim recites an intended use of the kit of claim 11 to be used in a method for detection of colon cancer or colon cancer precursor cells. While this intended use carries no patentable weight, Ferrie et al. teach use of primer sequences for the detection of colorectal cancer which includes both colon and rectal cancers (as given in Table 1 above and see also p. 1 lines 10-22).

Ferrie et al. expressly disclose the identical nucleic acid sequence presented in SEQ ID NO: 11 and 12 of the instant disclosure. It is noted that the instant primer sites of SEQ ID NOs: 11 and 12 are contained within the sequence disclosed by Ferrie et al.

The above described reference does not specifically disclose the identical primer sequences of SEQ ID NOs: 11 and 12, respectively, used in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

Art Unit: 1637

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the K-ras gene and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected

according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

15. Claims 7, 9, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coste et al. (1998), Nollet et al. (1996), Buck et al. (1999), and Stratagene (1988 catalog).

As claims 7 and 9 recite primers selected from a group of primers, these claims are rejected over prior art teaching at least two of the primers as follows.

Claims 7, 9, and 11 are rejected for SEQ ID NOs: 13 and 14, as described following. Coste et al. and in reference to Nollet et al. disclose amplification of DNA in the β -catenin gene with a primer sequences designed for amplification of detection of cancer including colon cancer (see Table 1 above and Abstract).

Further regarding claims 9 and 11, Coste et al. (see 3rd paragraph on p. 8848) and to Nollet et al. (see 1st paragraph on p. 417) suggest kits but do not provide motivation to place reagents including primers into kits.

Coste et al. expressly disclose the primer sequence which is primer PH2 and is identical to SEQ ID NO: 13 of the instant disclosure. Coste et al. reference Nollet et al. who expressly disclose the identical nucleic acid sequence presented in SEQ ID NO: 14 of the instant disclosure. It is noted that the instant primer site of SEQ ID NO: 14 is contained within the sequence disclosed by Nollet et al.

The above described reference does not specifically disclose the identical primer sequence of SEQ ID NO: 14, respectively, used in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the β -catenin gene and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked

Art Unit: 1637

(see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Regarding claim 9 and 11, Stratagene catalog teaches a motivation to combine reagents into kit format (page 39). It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Coste et al., Nollet et al., and Buck et al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far

more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

16. Claims 7, 9, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albertsen et al. (United States Patent 6,114,124 issued 2000) and Buck et al. (1999).

As claims 7 and 9 recite primers selected from a group of primers, these claims are rejected over prior art teaching at least two of the primers as follows.

Claims 7, 9, and 11 are rejected for SEQ ID NOs: 9 and 15 as described following. Albertsen et al. disclose amplification of DNA in the APC gene with primers designed for amplification of detection of colon cancer (see Table 1 above and see column 8 lines 13-20).

Further regarding claims 9 and 11, Albertsen et al. teach kits comprising probes/primers (see Abstract and column 9 lines 1-5). Further regarding claim 11, this claim recites an intended use of the kit of claim 9 to be used in a method for detection of colon cancer or colon cancer precursor cells. While this intended use carries no patentable weight, Albertsen et al. teach use of primer sequences for the detection of colon cancer (as given in Table 1 above and see column 8 lines 14-20).

Albertsen et al. expressly disclose the identical nucleic acid sequence presented

Art Unit: 1637

in SEQ ID NO: 9 and 15 of the instant disclosure. It is noted that the instant primer sites of SEQ ID NOs: 9 and 15 are contained within the sequence disclosed by Albertsen et al.

The above described reference does not specifically disclose the identical primer sequences of SEQ ID NOs: 9 and 15, respectively, used in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the APC gene and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at

issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

17. Claims 7, 9, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ikawa et al. (1988), and Buck et al. (1999).

As claims 7 and 9 recite primers selected from a group of primers, these claims are rejected over prior art teaching at least two of the primers as follows.

Claims 7, 9, and 11 are rejected for SEQ ID NOs: 17 and 18, as described following. Ikawa et al. disclose amplification of DNA in the B-raf gene with primers designed for amplification of detection of cancer including colon cancer (see Table 1 above and see Figure 1).

Further regarding claims 9 and 11, Ikawa et al. teach a kit comprising DNA fragments (see 2nd paragraph on p. 2651). Further regarding claim 11, this claim recites an intended use of the kit of claim 9 to be used in a method for detection of colon cancer or colon cancer precursor cells. While this intended use carries no patentable weight, Ikawa et al. teach use of primer sequences for the detection of cancer (as given in Table 1 above and see 1st paragraph on p. 2651).

Ikawa et al. expressly disclose the identical nucleic acid sequence presented in SEQ ID NO: 17 and 18 of the instant disclosure. It is noted that the instant primer sites of SEQ ID NOs: 17 and 18 are contained within the sequence disclosed by Ikawa et al.

The above described reference does not specifically disclose the identical primer sequences of SEQ ID NOs: 17 and 18, respectively, used in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious.

Regarding structural or functional homologs, however, the Court stated,
"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the B-raf gene and concerning which a biochemist of ordinary skill would attempt to obtain

alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

18. Claims 1, 4-6, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al. (1999, previously cited), Davies et al. (June 2002), Kmiec et al.

(WO200173002 published 2001), Shuber et al. (WO200118252 published 2001), Ferrie et al. (GB2327497 published 1999), Coste et al. (1998), Nollet et al. (1996), Albertsen et al. (United States Patent 6,114,124 issued 2000), Ikawa et al. (1988), and Buck et al. (1999).

As claim 1 is indefinite as to what primers are alternative, this claim is rejected for all primers of SEQ ID NOs: 1-18 as follows.

Regarding claim 1, Salahshor et al. teach methods for the non-invasive early detection of colon cancer or intestinal cancer precursor cells (entire publication) by means of mutational analysis of the genes for APC, K-ras, and β -catenin in a sample (see Table 1), characterized in that the method comprises the following steps: obtaining DNA from the sample (see the section *DNA extraction* on p. 248), performing an amplification reaction in the genes for APC, K-ras, and β -catenin, using primers to the genes for APC, K-ras, and β -catenin (see last paragraph on p. 248 continued through the 3rd full paragraph on p. 249), wherein amplification products are formed and performing a mutational analysis in the amplification products (entire article, especially Table 1).

Regarding claim 1, Salahshor et al. teach obtaining DNA but do not specifically teach collecting a stool sample and homogenizing the sample to obtain the DNA; do not specifically teach the B-raf gene; and do not specifically teach primers consisting of sequences of instant SEQ ID NOs; 1-18.

Regarding claim 1 Ikawa et al. teach methods for the non-invasive early

Art Unit: 1637

detection of cancer by means of mutational analysis of the genes for B-raf in a sample (entire article, especially the Title) and for the ras gene family (see 1st sentence on p. 2651), characterized in that the method comprises the following steps: obtaining DNA from the sample (see 2nd paragraph on p. 2651), performing an amplification reaction by synthesizing DNA in the genes for B-raf using primers (see Figure 1 and legend) and teach sequences comprising sequences of instant SEQ ID NOs: 17 and 18, wherein amplification products are formed and performing a mutational analysis in the amplification products (entire article especially Figure 1).

Regarding claim 1, Ikawa et al. teach detection of cancer and teach obtaining DNA but do not specifically teach collecting a stool sample and homogenizing the sample to obtain the DNA; do not specifically teach detection of colon cancer or intestinal cancer; do not specifically teach the APC and β-catenin genes; and do not teach sequences comprising sequences of instant SEQ ID NOs: 1-16.

Regarding claims 4 and 5, Ikawa et al. teach separation of colony amplification products by agarose gel electrophoresis (see 7th sentence of 2nd paragraph on p. 2651).

Regarding claim 1, Davies et al. teach methods for the non-invasive early detection of colorectal cancer by means of mutational analysis of the genes for B-raf (entire article, especially the Title), KRAS (see 4th sentence in the 3rd paragraph on p. 952) in a sample, characterized in that the method comprises the following steps: obtaining DNA from the sample (see 2nd paragraph on p. 949),

Art Unit: 1637

performing an amplification reaction using primers (see 2nd paragraph on p. 949), wherein amplification products are formed and performing a mutational analysis in the amplification products (entire article especially Figure 1).

Regarding claim 1, Davies et al. teach detection of colorectal cancer and teach obtaining DNA but do not specifically teach collecting a stool sample and homogenizing the sample to obtain the DNA; do not specifically teach the APC and β-catenin genes; and do not teach sequences comprising sequences of instant SEQ ID NOS: 1-18.

Regarding claims 5 and 6, Davies et al. teach detecting mutagenic conformation by isolating and sequencing both single strands (see the section *Mutation screening* on p. 953) in a sequence electropherogram (see Figure 1) obtained from capillary electrophoresis (see Title of reference no. 23 on p. 954).

Regarding claim 1, Shuber et al. teach methods for the non-invasive early detection of colon cancer or intestinal cancer precursor cells (entire publication, especially the Abstract) by means of mutational analysis of the genes for APC and other genes (see Example 3 on p. 20) in a sample, characterized in that the method comprises the following steps:

collecting a stool sample (see p. 16 line 14),
homogenizing the sample (see p. 16 line 14),
obtaining DNA from the sample (see p. 16 lines 22-33),
performing an amplification reaction in the genes for APC using primers (see Example 3 on p. 20).

Regarding claim 1, Shuber et al. do not specifically teach primers consisting of sequences of instant SEQ ID NOs; 1-5 and 8-18.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Salahshor et al. of mutational analysis of the genes genes for APC, K-ras, and β -catenin by including mutational analysis of the B-raf gene as suggested by Ikawa et al. and Davies et al. and by collecting and homogenizing a stool sample as suggested by Shuber et al. with a reasonable expectation of success. The motivation to do so is provided by Ikawa et al. and Davies et al., who as with Salahshor, teach detection of cancer and colorectal cancer by mutational analysis of ras genes; who teach that there is no activation of these ras genes in more than half the human tumors (see 1st sentence on p. 2651 of Ikawa et al.); and further teach that the mutational analysis of the B-raf oncogene thus improves the detection of cancer (see 1st paragraphs of both Ikawa et al. and Davies et al.). The motivation to use stool as sample is provided by Shuber et al. who teach that using stool for detection of colon cancer is an exemplary method for detection of colon cancer (see p. 16 lines 3). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Regarding claims 1, 7, 9, and 14 as shown in Table 1 above the references disclose sequences comprising the claimed nucleic acid sequences of SEQ ID NOs: 1-

Art Unit: 1637

18 as summarized below. Except that, Coste et al. specifically teach the nucleic acid sequence consisting of the claimed sequence of SEQ ID NO: 13.

- 1-5, 8, 10, and 16 Kmiec et al. (WO200173002 published 2001),
6 and 7 Shuber et al. (WO200118252 published 2001),
11 and 12 Ferrie et al. (GB2327497 published 1999),
13 Coste et al. (1998),
14 Nollet et al. (1996 and referenced by Coste et al.),
9 and 15 Albertsen et al. (United States Patent 6,114,124 issued 2000), and
17 and 18 Ikawa et al. (1988).

Claims 1, 7, 9, and 14 are rejected for SEQ ID NOs: 1-18, as described following.
With regard to Claim 1, 7, 9, and 14, 1-5, 8, 10, and 16, Kmiec et al., Shuber et al., Ferrie et al., Coste et al., Nollet et al., Albertsen et al., and Ikawa et al. disclose amplification of DNA with primers designed for amplification of genes containing mutations linked to colorectal cancer.

Kmiec et al., Shuber et al., Ferrie et al., Coste et al., Nollet et al., Albertsen et al., and Ikawa et al. expressly disclose the identical nucleic acid sequences presented in SEQ ID NO: 1-18 of the instant disclosures as given above. It is noted that the instant primer sites of SEQ ID NOs: 1-12 and 14-18 are contained within the sequence disclosed by Kmiec et al., Shuber et al., Ferrie et al., Nollet et al., Albertsen et al., and

Ikawa et al. Coste et al. specifically teach the sequence consisting of the claimed sequence of SEQ ID NO: 13.

The above described references with exception of Coste et al. do not specifically disclose the identical primer sequences of SEQ ID NOs: 1-12 and 14-18, the primers used in the claimed invention. Coste et al. specifically teach the sequence consisting of the claimed sequence of SEQ ID NO: 13.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious.

Regarding structural or functional homologs, however, the Court stated, "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the amplification of genes associated with colorectal cancer and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532,

column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Furthermore as given above, at least Salahshor et al., Ikawa et al., Davies et al., and Shuber et al. provide the motivation to perform amplification of the known genes for APC, K-ras, β -catenin, and B-raf for the detection of colorectal cancer. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

19. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al. (1999, previously cited), Davies et al. (June 2002), Kmiec et al. (WO200173002 published 2001), Shuber et al. (WO200118252 published 2001), Ferrie et al. (GB2327497 published 1999), Coste et al. (1998), Nollet et al. (WO2002058534 published 1 August 2002), Albertsen et al. (United States Patent 6,114,124 issued 2000), Ikawa et al. (1988), and Buck et al. (1999) as applied to claim 1 above, and further in view of Gerry et al. (1999).

Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., and Buck et al. teach as noted above.

Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., and Buck et al. do not specifically teach methods using DNA chips.

Regarding claim 2, Gerry et al. teach methods characterized in that the detection of mutations in selected sections of the genes for K-ras and other genes is effected by means of a DNA chip which is a DNA microchip, said DNA chip including probes for K-ras (entire article, especially the Abstract)

Regarding claim 2, Gerry et al. teach methods for detection of the K-ras gene and other genes but does not specifically teach detection of the genes of APC, β -catenin, and B-raf and do not specifically teach the primers of claim 1.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Salahshor et al., Davies et al., Kmiec et al., Shuber et al., Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., and Buck et al. by using DNA microchips as suggested by Gerry et al. with a reasonable expectation of success. The motivation to do so is provided by Gerry et al. who teach: "Thus, a single array design can be programmed to detect a wide range of genetic mutations. Robust methods for the rapid detection of mutations at numerous potential sites in multiple genes hold great promise to improve the diagnosis and treatment of cancer patients" (see 1st two full sentences on p. 259). Furthermore Gerry et al. teach the methods are applicable to known multiple genes and specifically to the K-ras gene, and as Salahshor et al., Davies et al., Kmiec et al., Shuber et al., Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., and Buck et al. in combination teach detection of the known multiple genes of APC, K-ras, β-catenin, and B-raf; it would have been obvious to one of ordinary skill in the art at the time of claimed invention to use the DNA microchip methods of Gerry et al. for detection of the known multiple genes of APC, K-ras, β-catenin, and B-raf. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

20. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al. (1999, previously cited), Davies et al. (June 2002), Kmiec et al. (WO200173002 published 2001), Shuber et al. (WO200118252 published 2001), Ferrie et al. (GB2327497 published 1999), Coste et al. (1998), Nollet et al. (WO2002058534

Art Unit: 1637

published 1 August 2002), Albertsen et al. (United States Patent 6,114,124 issued 2000), Ikawa et al. (1988), and Buck et al. (1999) as applied to claim 1 above, and further in view of Shuber et al. (WO199858081 published 1998).

Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., and Buck et al. teach as noted above.

Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., and Buck et al. do not specifically teach methods using magnetic beads.

Regarding claim 3, Shuber et al. (1998) teach methods characterized in that the K-ras and other genes are accumulated from total DNA by hybridizing sequence-specific biotinylated oligonucleotides with the genes for K-ras (see p. 6 lines 24 and 25 for capture of the kras gene) using coupling of the biotin residue to streptavidin and subsequent separation via magnetic particles (see p. 5 line 25 to p. 6 line 2 and see entire p. 9).

Regarding claim 3, Shuber et al. (1998) teach methods for detection of the K-ras gene and other genes but does not specifically teach detection of the genes of APC, β -catenin, and B-raf and do not specifically teach the primers of claim 1.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Salahshor et al., Davies

Art Unit: 1637

et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., and Buck et al. by using biotinylated probes with streptavidin coated magnetic beads as suggested by Shuber et al. (1998) with a reasonable expectation of success. The motivation to do so is provided by Shuber et al. (1998) who teach that these methods produce increased yields of DNA from stool, thereby allowing more efficient sequence-specific capture of target nucleic acids. Furthermore Shuber et al. (1998) teaches the methods are applicable to known genes in general and specifically to the kras gene, and as Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., and Buck et al. in combination teach detection of the known genes of APC, K-ras, β -catenin, and B-raf; it would have been obvious to one of ordinary skill in the art at the time of claimed invention to use the methods of Shuber et al. (1998) for detection of the known genes of APC, K-ras, β -catenin, and B-raf. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

21. Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al. (1999, previously cited), Davies et al. (June 2002), Kmiec et al. (WO200173002 published 2001), Shuber et al. (WO200118252 published 2001), Ferrie et al. (GB2327497 published 1999), Coste et al. (1998), Nollet et al. (WO2002058534 published 1 August 2002), Albertsen et al. (United States Patent 6,114,124 issued 2000), Ikawa et al. (1988), and Buck et al. (1999) as applied to claim 1 above, and further in view of Baba et al. (1996).

Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., and Buck et al. teach as noted above.

Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., and Buck et al. do not specifically teach HPLC or SSCP techniques.

Regarding claims 12 and 13, Baba et al. teach methods of detecting disease by analysis of disease causing genes including colon cancer causing genes and other genes (see Title and Table 3) including applying analysis techniques to detection of K-ras oncogene mutations (see last sentence on p. 286 continued to p. 287), teach an electrophoretic technique of SSCP which is capillary electrophoresis applied to SSCP analysis of the p53 gene (see section 4.3 SSCP on p. 287) and teach that a chromatographic procedure can be used which are reverse phase and ion-exchange HPLC (see 1st paragraph under section 5.2 *Monitoring of DNA* on p. 296).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., and Buck et al. by using an SSCP electrophoretic technique or an HPLC chromatographic procedure as suggested by Baba et al. with a reasonable expectation of success. The motivation to do so is provided by Baba et al. who teach that: "SSCP analysis using capillary electrophoresis has also been

Art Unit: 1637

successfully applied to the detection of the mutation on K-ras oncogene . . ." (see 1st sentence of 2nd paragraph on p. 290) and can successfully detect mutations with reverse phase and ion exchange HPLC . Furthermore Baba et al. teach the methods are applicable to known genes in general and specifically to the K-ras gene, and as Salahshor et al., Davies et al., Kmiec et al., Shuber et al., Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., and Buck et al. in combination teach detection of the known genes of APC, K-ras, β -catenin, and B-raf; it would have been obvious to one of ordinary skill in the art at the time of claimed invention to use the methods of Baba et al. for detection of the known genes of APC, K-ras, β -catenin, and B-raf. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

22. No claim is free of the prior art.
23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 7:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Mark Staples/
Examiner, Art Unit 1637
May 22, 2009